

07/13/2006 10748085b.trn

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NEWS 4 APR 04 STN AnaVist \$500 visualization usage credit offered
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NEWS 6 MAY 11 KOREPAT updates resume
NEWS 7 MAY 19 Derwent World Patents Index to be reloaded and enhanced
NEWS 8 MAY 30 IPC 8 Rolled-up Core codes added to CA/CAplus and
USPATFULL/USPAT2
NEWS 9 MAY 30 The F-Term thesaurus is now available in CA/CAplus
NEWS 10 JUN 02 The first reclassification of IPC codes now complete in
INPADOC
NEWS 11 JUN 26 TULSA/TULSA2 reloaded and enhanced with new search and
and display fields
NEWS 12 JUN 28 Price changes in full-text patent databases EPFULL and PCTFULL
NEWS 13 JUL 07 Coverage of Research Disclosure reinstated in DWPI
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NEWS EXPRESS JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0JC(JP), AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

NEWS HOURS STN Operating Hours Plus Help Desk Availability
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07/13/2006 10748085b.trn

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STRUCTURE FILE UPDATES: 12 JUL 2006 HIGHEST RN 892389-74-1
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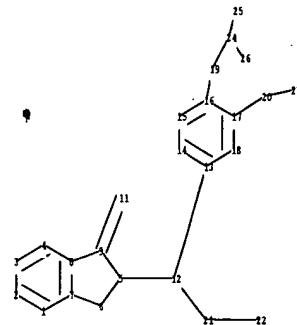
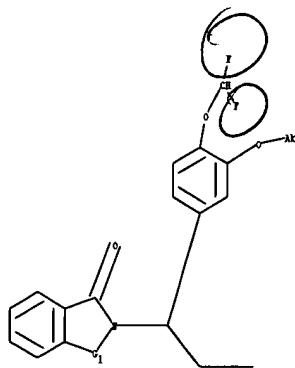
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REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

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=>
Uploading C:\Program Files\Stnexp\Queries\10748085b.str



chain nodes :

11 12 19 20 21 22 24 25 26 27

ring nodes :

1 2 3 4 5 6 7 8 9 13 14 15 16 17 18

chain bonds :

5-12 9-11 12-13 12-21 16-19 17-20 19-24 20-27 21-22 24-25 24-26

ring bonds :

1-2 1-7 2-3 3-4 4-8 5-6 5-9 6-7 7-8 8-9 13-14 13-18 14-15 15-16 16-17
17-18

exact/norm bonds :

5-6 5-9 5-12 6-7 8-9 9-11 12-13 12-21 16-19 17-20 19-24 20-27 21-22
24-25 24-26

normalized bonds :

1-2 1-7 2-3 3-4 4-8 7-8 13-14 13-18 14-15 15-16 16-17 17-18

isolated ring systems :

containing 1 : 13 :

G1:CH2,SO2,C(O)CH3

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 11:CLASS
12:CLASS 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:CLASS 20:CLASS
21:CLASS 22:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS

L1 STRUCTURE UPLOADED

=> d 11

07/13/2006 10748085b.trn

L1 HAS NO ANSWERS
L1 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.

=> S 11
SAMPLE SEARCH INITIATED 08:03:29 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 3 TO ITERATE

100.0% PROCESSED 3 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 3 TO 163
PROJECTED ANSWERS: 2 TO 124

L2 2 SEA SSS SAM L1

=> S 11 SSS full
FULL SEARCH INITIATED 08:03:35 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 48 TO ITERATE

100.0% PROCESSED 48 ITERATIONS 25 ANSWERS
SEARCH TIME: 00.00.01

L3 25 SEA SSS FUL L1

=> FIL HCAPLUS
COST IN U.S. DOLLARS SINCE FILE TOTAL
SESSION
FULL ESTIMATED COST ENTRY 166.94 167.15

FILE 'HCAPLUS' ENTERED AT 08:03:41 ON 13 JUL 2006
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FILE COVERS 1907 - 13 Jul 2006 VOL 145 ISS 3
FILE LAST UPDATED: 12 Jul 2006 (20060712/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 13

L4

-1 L3

=> d 14 ibib abs hitstr tot

L4 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:589381 HCAPLUS

DOCUMENT NUMBER: 141:140314

TITLE: Preparation of 2-(fluoroalkoxyphenylalkyl)-1,3-dihydroisoindolones as PDE4, TNF- α , and/or MMP inhibitors

INVENTOR(S): Muller, George W.; Man, Hon-Wah; Zhang, Weihong

PATENT ASSIGNEE(S): Celgene Corporation, USA

SOURCE: PCT Int. Appl., 98 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

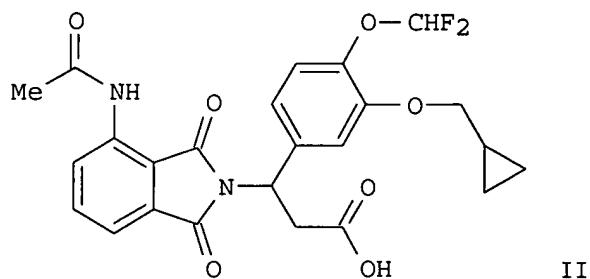
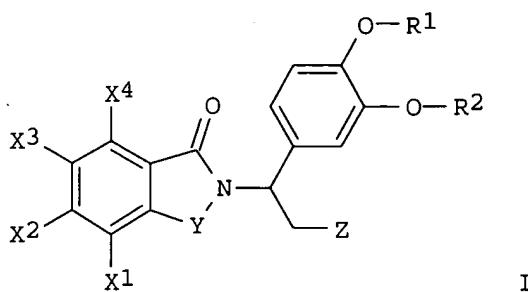
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2004060313 | A2 | 20040722 | WO 2003-US41568 | 20031229 |
| WO 2004060313 | A3 | 20050915 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2511843 | AA | 20040722 | CA 2003-2511843 | 20031229 |
| AU 2003303511 | A1 | 20040729 | AU 2003-303511 | 20031229 |
| US 2004204448 | A1 | 20041014 | US 2003-748085 | 20031229 |
| EP 1587474 | A2 | 20051026 | EP 2003-808605 | 20031229 |
| EP 1587474 | A3 | 20051102 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| BR 2003017885 | A | 20051206 | BR 2003-17885 | 20031229 |
| JP 2006515310 | T2 | 20060525 | JP 2004-565816 | 20031229 |
| PRIORITY APPLN. INFO.: | | | US 2002-436975P | P 20021230 |
| | | | WO 2003-US41568 | W 20031229 |

OTHER SOURCE(S): MARPAT 141:140314

GI

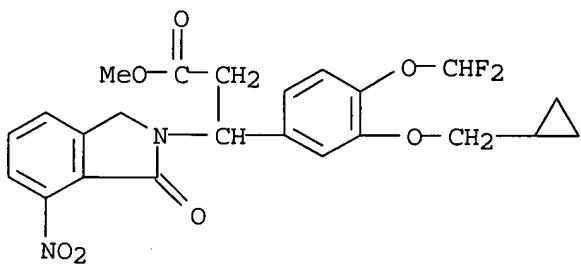


AB Title compds. I [wherein X1-X4 = independently H, halo, NO₂, NH₂, CF₃, alkyl, cycloalkyl(alkyl), NR₇R₈-(alkyl), R₈CONH-(alkyl), NR₇R₈CONH-(alkyl), R₈OCONH-(alkyl), R₈O-(alkyl), imidazolyl(alkyl), pyrrolyl(alkyl), oxadiazolyl(alkyl), triazolyl(alkyl); or X1 and X2 or X2 and X3 or X3 and X4 may be taken together to form a (hetero)cycloalkyl ring; Y = CO, CH₂, CH₂CO, COCH₂, SO₂; Z = H, COR₃, alkylsulfonyl(alkyl), alkyl, CH₂OH, alkoxy methyl, CN; R₁ and R₂ = independently CHF₂, alkyl, cycloalkyl(alkyl); at least one of R₁ and R₂ = CHF₂; R₃ = NR₄R₅, alkyl, OH, alkoxy, (un)substituted Ph, PhCH₂; R₄ and R₅ = independently H, alkyl, OH, OCOR₆; R₆ = alkyl(amino), Ph, PhCH₂, aryl; R₇ and R₈ = independently H, alkyl, cycloalkyl(alkyl), NR₇R₈-alkyl, R₈O-alkyl, Ph, PhCH₂, aryl; or pharmaceutically acceptable salts, hydrates, solvates, clathrates, stereoisomers, and prodrugs thereof] were prepared. For example, alkylation of 3,4-dihydroxybenzaldehyde with chlorodifluoromethane in the presence of K₂CO₃ in DMF gave 4-difluoromethoxy-3-hydroxybenzaldehyde (15%), which was further alkylated with bromomethylcyclopropane under the same conditions to afford 3-cyclopropylmethoxy-4-difluoromethoxybenzaldehyde (100%). Reaction of the benzaldehyde with ammonium acetate in 95% EtOH, followed by addition of malonic acid provided 3-amino-3-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)propionic acid (52%). Condensation of the amine with 3-acetamidophthalic anhydride using sodium acetate in AcOH yielded the isoindoledione II (85%). I and their pharmaceutical compns., optionally in combination with another therapeutic agent, are useful for the treatment or prevention of diseases associated with phosphodiesterase 4 (PDE4) inhibition, abnormal tumor necrosis factor α (TNF- α) levels, and/or matrix metalloproteinase (MMP) inhibition, such as myelodysplastic syndrome, myeloproliferative disease, complex regional pain syndrome, cancer, inflammatory diseases, and autoimmune diseases (no data).

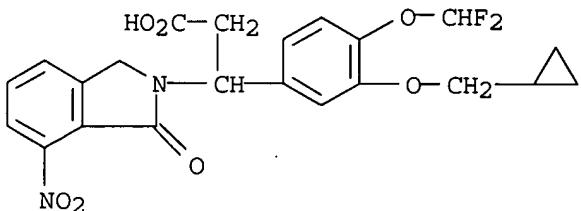
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 725256-77-9P, 3-[3-(Cyclopropylmethoxy)-4-difluoromethoxyphenyl]-3-(7-nitro-1-oxo-1,3-dihydroisoindol-2-yl)propionic acid
 725256-78-0P, 3-[3-(Cyclopropylmethoxy)-4-difluoromethoxyphenyl]-3-

(7-nitro-1-oxo-1,3-dihydroisoindol-2-yl)-N,N-dimethylpropionamide
 725256-83-7P, 3-[7-(Cyclopropylcarbonylamino)-1-oxo-1,3-dihydroisoindol-2-yl]-3-(4-difluoromethoxy-3-ethoxyphenyl)propionic acid methyl ester 725256-84-8P, 3-(7-Amino-1-oxo-1,3-dihydroisoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxyphenyl)propionic acid methyl ester 725256-85-9P, 3-(7-Acetylamino-1-oxo-1,3-dihydroisoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxyphenyl)propionic acid methyl ester 725256-86-0P, 3-[7-(Acetylamino)-1-oxo-1,3-dihydroisoindol-2-yl]-3-(4-difluoromethoxy-3-ethoxyphenyl)propionic acid 725256-87-1P, 3-[7-(Cyclopropylcarbonylamino)-1-oxo-1,3-dihydroisoindol-2-yl]-3-(4-difluoromethoxy-3-ethoxyphenyl)propionic acid 725257-12-5P, 3-[3,4-Bis(difluoromethoxy)phenyl]-3-[7-(cyclopropylcarbonylamino)-1-oxo-1,3-dihydroisoindol-2-yl]propionic acid
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (PDE4, TNF- α , and/or MMP inhibitor; preparation of (fluoroalkoxyphenylalkyl)isoindolones as PDE4, TNF- α , and/or MMP inhibitors for treatment of inflammatory diseases, autoimmune diseases, cancer, and pain)

RN 725256-76-8 HCPLUS

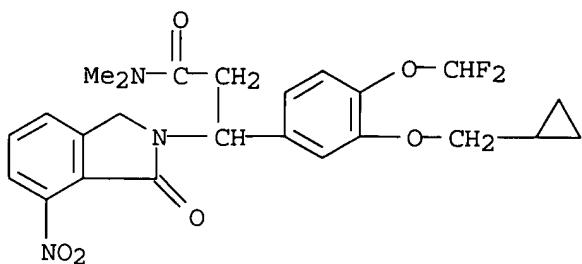
CN 2H-Isoindole-2-propanoic acid, β -[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl]-1,3-dihydro-7-nitro-1-oxo-, methyl ester (9CI) (CA INDEX NAME)

RN 725256-77-9 HCPLUS

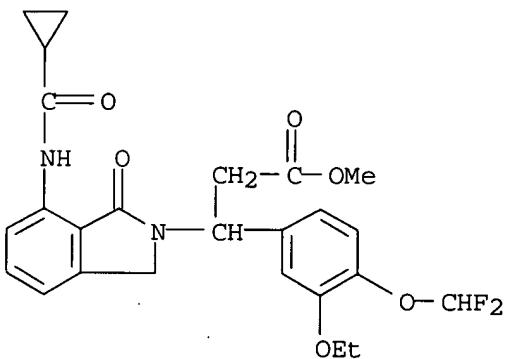
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RN 725256-78-0 HCPLUS

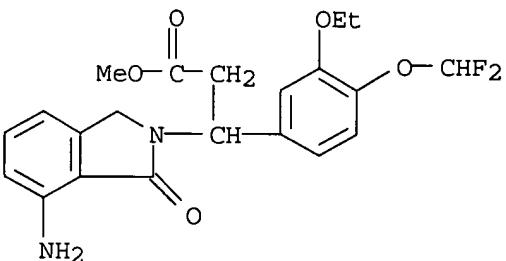
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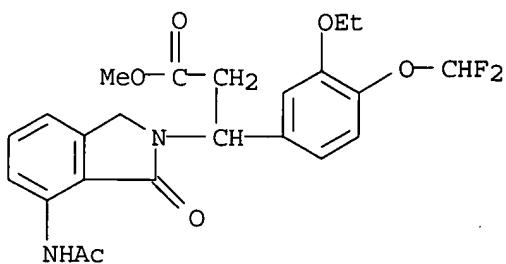
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 (CA INDEX NAME)



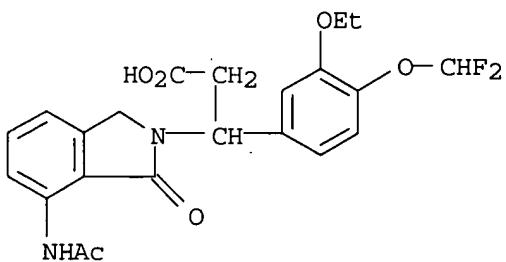
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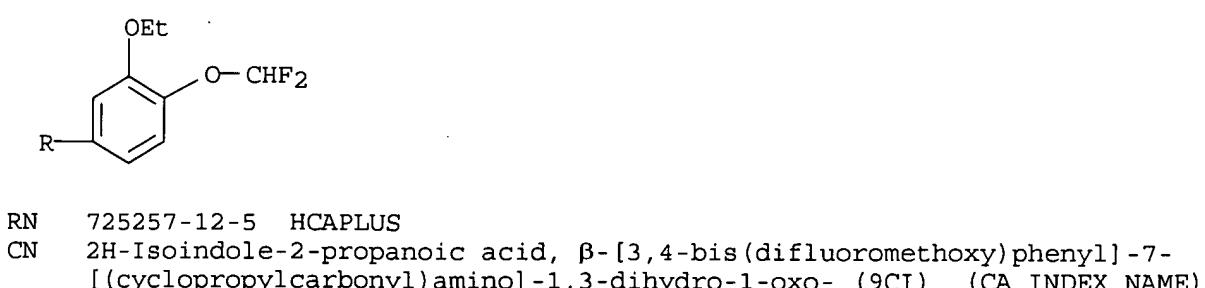
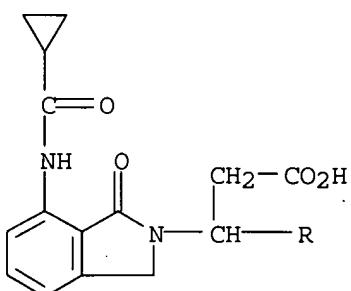
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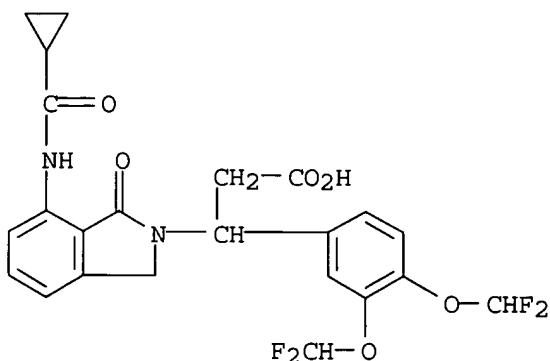


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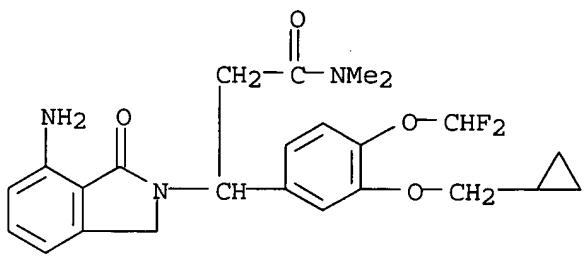


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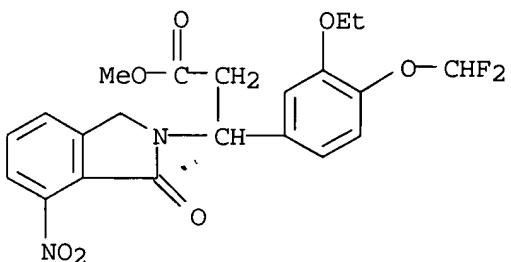




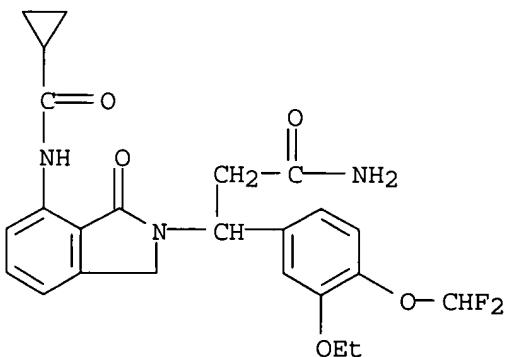
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 725256-82-6P, 3-(4-Difluoromethoxy-3-ethoxyphenyl)-3-(7-nitro-1-oxo-1,3-dihydroisoindol-2-yl)propionic acid methyl ester
 725256-88-2P, Cyclopropanecarboxylic acid N-[2-[2-carbamoyl-1-(4-difluoromethoxy-3-ethoxyphenyl)ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl]amide
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 725256-91-7P, 3-(7-Acetylamino-1-oxo-1,3-dihydroisoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxyphenyl)propionamide
 725256-92-8P, 3-(7-Acetylamino-1-oxo-1,3-dihydroisoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxyphenyl)-N,N-dimethylpropionamide
 725256-93-9P, 3-(7-Acetylamino-1-oxo-1,3-dihydroisoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxyphenyl)-N-hydroxypropionamide
 725257-02-3P, Cyclopropanecarboxylic acid N-[2-[2-carbamoyl-1-(4-difluoromethoxy-3-ethoxyphenyl)ethyl]-7-chloro-3-oxo-2,3-dihydro-1H-isoindol-4-yl]amide
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 725257-11-4P, Cyclopropanecarboxylic acid N-[2-[1-[3,4-bis(difluoromethoxy)phenyl]-2-(dimethylcarbamoyl)ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl]amide
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 725257-14-7P, Cyclopropanecarboxylic acid N-[2-[1-[3,4-bis(difluoromethoxy)phenyl]-2-hydroxycarbamoylethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl]amide
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (PDE4, TNF- α , and/or MMP inhibitor; preparation of fluoroalkoxyphenylalkyl)isoindolones as PDE4, TNF- α , and/or MMP inhibitors for treatment of inflammatory diseases, autoimmune diseases, cancer, and pain)
- RN 725256-79-1 HCPLUS
- CN 2H-Isoindole-2-propanamide, 7-amino- β -[3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl]-1,3-dihydro-N,N-dimethyl-1-oxo- (9CI) (CA INDEX NAME)



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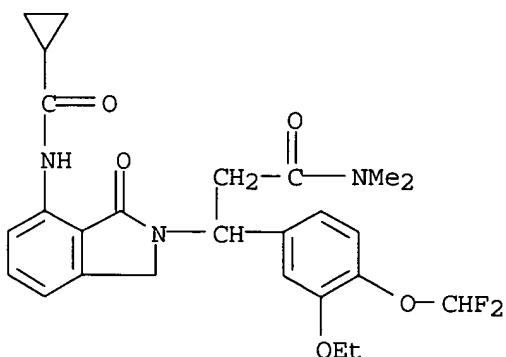
CN 2H-Isoindole-2-propanoic acid, β -[4-(difluoromethoxy)-3-ethoxyphenyl]-1,3-dihydro-7-nitro-1-oxo-, methyl ester (9CI) (CA INDEX NAME)

RN 725256-88-2 HCPLUS

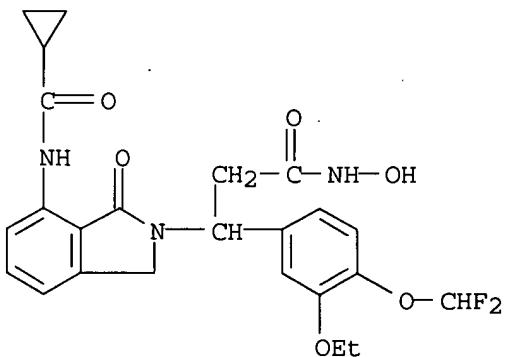
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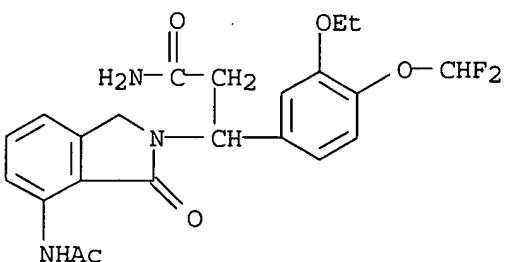
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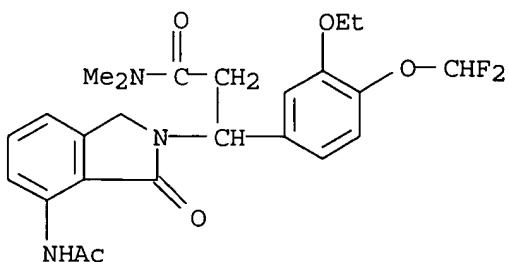
RN 725256-90-6 HCPLUS
CN 2H-Isoindole-2-propanamide, 7-[(cyclopropylcarbonyl)amino]-β-[4-(difluoromethoxy)-3-ethoxyphenyl]-1,3-dihydro-N-hydroxy-1-oxo- (9CI) (CA INDEX NAME)



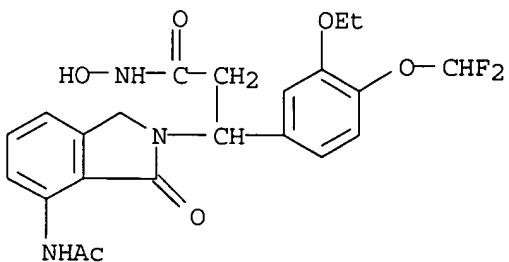
RN 725256-91-7 HCPLUS
CN 2H-Isoindole-2-propanamide, 7-(acetylamino)-β-[4-(difluoromethoxy)-3-ethoxyphenyl]-1,3-dihydro-1-oxo- (9CI) (CA INDEX NAME)



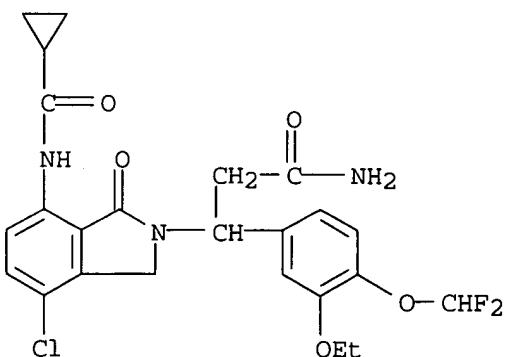
RN 725256-92-8 HCPLUS
CN 2H-Isoindole-2-propanamide, 7-(acetylamino)-β-[4-(difluoromethoxy)-3-ethoxyphenyl]-1,3-dihydro-N,N-dimethyl-1-oxo- (9CI) (CA INDEX NAME)



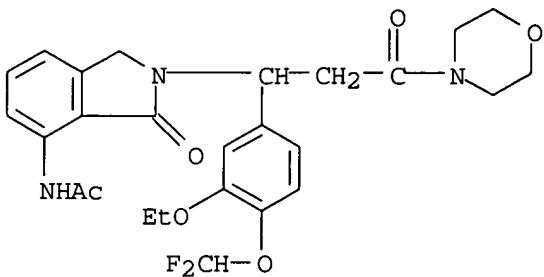
RN 725256-93-9 HCAPLUS
 CN 2H-Isoindole-2-propanamide, 7-(acetylamino)- β -[4-(difluoromethoxy)-3-ethoxyphenyl]-1,3-dihydro-N-hydroxy-1-oxo- (9CI) (CA INDEX NAME)



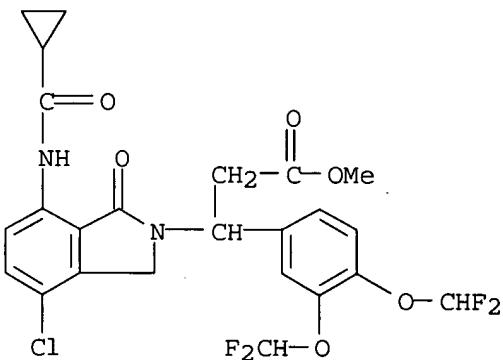
RN 725257-02-3 HCAPLUS
 CN 2H-Isoindole-2-propanamide, 4-chloro-7-[(cyclopropylcarbonyl)amino]- β -[4-(difluoromethoxy)-3-ethoxyphenyl]-1,3-dihydro-1-oxo- (9CI) (CA INDEX NAME)



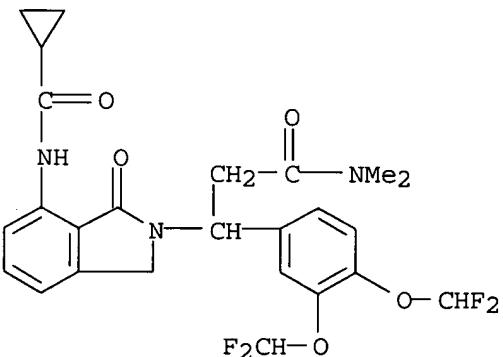
RN 725257-05-6 HCAPLUS
 CN Acetamide, N-[2-[1-[4-(difluoromethoxy)-3-ethoxyphenyl]-3-(4-morpholinyl)-3-oxopropyl]-2,3-dihydro-3-oxo-1H-isoindol-4-yl]- (9CI) (CA INDEX NAME)



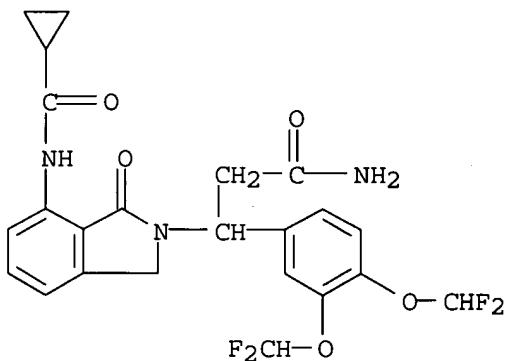
RN 725257-08-9 HCPLUS
 CN 2H-Isoindole-2-propanoic acid, β -[3,4-bis(difluoromethoxy)phenyl]-4-chloro-7-[(cyclopropylcarbonyl)amino]-1,3-dihydro-1-oxo-, methyl ester (9CI) (CA INDEX NAME)



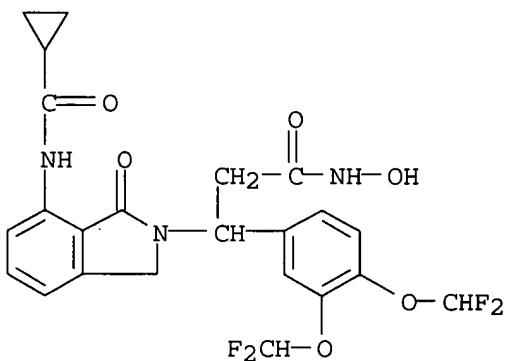
RN 725257-11-4 HCPLUS
 CN 2H-Isoindole-2-propanamide, β -[3,4-bis(difluoromethoxy)phenyl]-7-[(cyclopropylcarbonyl)amino]-1,3-dihydro-N,N-dimethyl-1-oxo- (9CI) (CA INDEX NAME)



RN 725257-13-6 HCPLUS
 CN 2H-Isoindole-2-propanamide, β -[3,4-bis(difluoromethoxy)phenyl]-7-[(cyclopropylcarbonyl)amino]-1,3-dihydro-1-oxo- (9CI) (CA INDEX NAME)

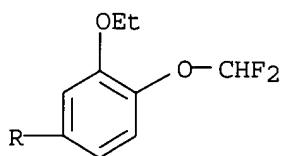
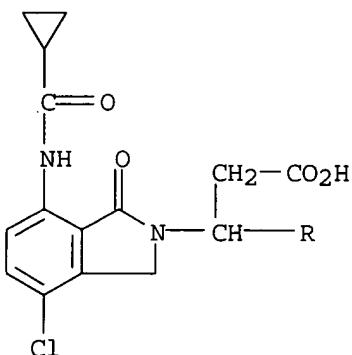


RN 725257-14-7 HCPLUS

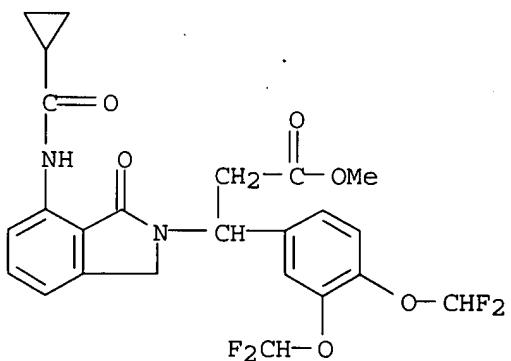
CN 2H-Isoindole-2-propanamide, β -[3,4-bis(difluoromethoxy)phenyl]-7-[(cyclopropylcarbonyl)amino]-1,3-dihydro-N-hydroxy-1-oxo- (9CI) (CA INDEX NAME)IT 725257-03-4, 3-[4-Chloro-7-(cyclopropylcarbonylamino)-1-oxo-1,3-dihydroisoindol-2-yl]-3-(4-difluoromethoxy-3-ethoxyphenyl)propionic acid
725257-15-8, 3-[3,4-Bis(difluoromethoxy)phenyl]-3-[7-(cyclopropylcarbonylamino)-1-oxo-1,3-dihydroisoindol-2-yl]propionic acid methyl esterRL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of (fluoroalkoxyphenylalkyl)isoindolones as PDE4, TNF- α , and/or MMP inhibitors for treatment of inflammatory diseases, autoimmune diseases, cancer, and pain)

RN 725257-03-4 HCPLUS

CN 2H-Isoindole-2-propanoic acid, 4-chloro-7-[(cyclopropylcarbonyl)amino]- β -[4-(difluoromethoxy)-3-ethoxyphenyl]-1,3-dihydro-1-oxo- (9CI) (CA INDEX NAME)



RN 725257-15-8 HCAPLUS
 CN 2H-Isoindole-2-propanoic acid, β -[3,4-bis(difluoromethoxy)phenyl]-7-[(cyclopropylcarbonyl)amino]-1,3-dihydro-1-oxo-, methyl ester (9CI) (CA INDEX NAME)



| | | |
|--|------------|---------|
| => log Y | | |
| COST IN U.S. DOLLARS | SINCE FILE | TOTAL |
| FULL ESTIMATED COST | ENTRY | SESSION |
| | 10.17 | 177.32 |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE | TOTAL |
| CA SUBSCRIBER PRICE | ENTRY | SESSION |
| | -0.75 | -0.75 |

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